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EXAMINER

BOESEN, AGNIESZKA

ART UNIT PAPER NUMBER

1648

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/766,773

Applicant(s)

LAROSA ET AL.

Examiner

Agnieszka Boesen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 55 is/are allowed.
- 6) ☒ Claim(s) 36-54, and 56-58 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/19/05; 1/27/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received July 20, 2006.

Election/Restrictions

Applicant's election of group IX, claims 36 and 37 and species of rheumatoid arthritis is acknowledged. Applicants point out that claims 36, 50, 54, and 56-58 read on elected species of rheumatoid arthritis. Examiner agrees that claims 36, 50, 54, 56-58 and also claim 49 read on elected species of rheumatoid arthritis. Upon further consideration, and because no prior art have been be found that anticipates or renders obvious the elected species of rheumatoid arthritis, claims 38-48, 51-53, and 55 are examined. Thus, claims 36-58 are pending and under examination.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Thus the restriction requirement is deemed proper and is made FINAL.

Priority

Acknowledgment is made for priority to a DIV application, 09/497,625, which is a US Patent 6,727,349, which is a CIP of 09/359,193, which is a US Patent 6,352,832, which is a CIP of 09/121,781, which is a US Patent 6,312,689.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36, 37, 49, 50, 51, 54, and 56-58 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 7, 8, and 41-43 of U.S. Patent No. 6,312,689 B1 in view of Owens et al. (Journal of Immunological Methods, 1994).

Claims are drawn to a method of treating a CCR2-mediated disorder in a patient comprising administering to the patient an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2. The disorder is an inflammatory, autoimmune disorder such as multiple sclerosis, rheumatoid arthritis, atherogenesis and atherosclerosis.

Claims 6, 7, 8, 12 and 41-43 of U.S. Patent No. 6,312,689 B1 teach a method of treating a CCR2-mediated disorder in a patient comprising administering to the patient an effective amount of immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, wherein the disorder is an autoimmune disorder such as multiple sclerosis, rheumatoid arthritis, atherogenesis and atherosclerosis. The antibody is a human antibody or fragment thereof.

Claims 6, 7, 8, 12 and 41-43 of U.S. Patent No. 6,312,689 B1 do not expressly teach using humanized immunoglobulin/antibody in the method of treating rheumatoid arthritis. Owens et al. teach humanized immunoglobulin and discusses technologies used to generate humanized antibodies as well as the advantages of using humanized versus mouse antibodies in human therapy (see the entire document, particularly page 149 and 150). Owens et al. teach that use of rodent antibodies in human therapy poses a number of problems such as for example immunogenicity of the rodent antibodies and generation of undesired human anti-mouse antibodies in human (see page 149). Therefore it would have been obvious to the person of ordinary skill in the art to generate humanized immunoglobulin for therapeutic use in humans.

One would have been motivated to use Owens' humanized immunoglobulin in the method of treating rheumatoid arthritis taught in claims 6, 7, 8, 12 and 41 of U.S. Patent No. 6,312,689 B1, in order to avoid generation of anti-mouse antibodies in a human treated with mouse antibodies. One would have been motivated to use genetic engineering technique to generate humanized immunoglobulin for therapeutic use in human, because the technique allows for tailoring the antibody for particular use and also it allows production of large quantities of antibodies whereas human hybridomas are often unstable and are poor producers of human immunoglobulin (see Owens page 150).

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One would have had a reasonable expectation of success to generate a humanized immunoglobulin because the genetic engineering techniques used for production of humanized antibodies are well established in the art (see Owens page 160, Summary and conclusions).

Claims 36-48, and 52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-72 of U.S. Patent No. 6,352,832 B1 as follows, instant claims 36-38 over patent claims 1, 3; 26-29; instant claim 39 over patent claim 5; instant claims 40-42 over patent claims 6-8; instant claim 43 over patent claim 9, instant claim 44 over patent claim 13; instant claim 45 over patent claim 15; instant claim 46 over patent claim 14; instant claims 47 and 48 over patent claims 15 and 16. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because, in the case of instant claims 36-48, and 52, they are generic to all that is recited in the respective claims of the patent, i.e., the patented claims fall entirely within the scope of each of instant claims 36-48, and 52.

Claims are drawn to a method of treating a CCR2-mediated disorder in a patient comprising administering to the patient an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2. The disorder is an inflammatory disorder such as restenosis. Claims 1-72 of U.S. Patent No. 6,352,832 B1 disclose a method of inhibiting restenosis in a patient comprising administering to the patient an effective

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amount of humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of treating a CCR2-mediated disorder in a patient comprising administering to the patient an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, wherein the disorder is HIV infection. The specification does not sufficiently support the claimed method. There is insufficient evidence that administration of a humanized immunoglobulin having binding specificity for CCR2 would correlate with *in vivo* efficacy in humans resulting in successful treatment of HIV infection.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or

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the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) Scope or breadth of the claims

The claims are drawn to a method of treating HIV infection comprising administering to the patient an effective amount of a humanized immunoglobulin having binding specificity for CCR2. The specification contemplates use of antibodies with binding specificity for CCR2 for inhibition of HIV infection of a cell expressing mammalian CCR2 (see page 73, lines 18-23). The specification lacks the enabling disclosure with regard to methods of treating HIV infection comprising administering to the patient an effective amount of a humanized immunoglobulin having binding specificity for CCR2.

2) Nature of the invention

The nature of the invention is directed to a method of treating HIV infection.

3) Relative level of skill possessed by one of ordinary skill in the art

The relative level of skill possessed by one of ordinary skill in the art of medical research is relatively high, as a majority of lead investigators conducting scientific research and development in this particular technological area possess an M.D. and/or a Ph.D. in a scientific discipline such as virology, immunology, biochemistry, pharmacology, biology or the like.

4) State of, or the amount of knowledge in, the prior art

The obstacles to developing a successful therapy of HIV are well documented in the literature. These obstacles include 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with the respect to the gene encoding the envelope protein. 2) The fact that the mode of viral transmission includes both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission. 3) The establishment of a latent viral infection. 4) The ability of the virus to evade the immune responses in the central nervous system due to the blood-brain barrier. 5) The complexity and variation of the pathology of HIV infection in different individuals. 6) The inability of a natural infection to one strain of HIV to protect an individual from being infected with another strain of HIV (Machuca et al. Intervirology 1998, see discussion). These obstacles establish that the contemporary knowledge in the art would not allow the skilled artisan to use the claimed method to treat HIV infection without undue experimentation. Applicants have not provided any convincing evidence that their claimed method is indeed useful in treatment of HIV infection and have not provided sufficient guidance in to allow one skilled in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

5) Level or degree of predictability, or a lack thereof, in the art

The successes as well as failures of various approaches in the field of treatment of HIV infection have been summarized by McMichael and Hanke, HIV vaccines 1983-2003. Nature Medicine 2003, Vol. 9, p.875-880. Although, animal models are an essential resource for evaluating the safety and comparative efficacy of HIV therapeutics, the animal models cannot determine whether a candidate therapeutic will be effective in treatment of HIV infection of

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humans. The assurance of usefulness of candidate therapeutics can only be established in Phase II trials (Feinberg et al. Aids Vaccine Models : challenging challenge viruses. Nature Medicine, 2002, Vol. 8, pages 207-210).

Although clinical trials regarding HIV therapy using monoclonal antibodies for inhibition of chemokine receptor such as CCR5, have shown positive results (Business Wire, p. 1-4), clinical trials would need to be conducted in order to positively correlate that monoclonal antibodies blocking CCR2 receptor would indeed be efficacious in treatment of HIV infection. The use of monoclonal antibodies as therapeutics is associated with obstacles concerning their *in vivo* delivery. Pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In the instant case the antibodies, which are proteins can be destroyed before they are delivered to the site of antibody-receptor interaction.

6) Amount of guidance or direction provided by the inventor

Current specification contemplates evaluation of the capability of monoclonal antibodies with specificity to CCR2 to inhibit binding and infection of HIV to a cell *in vitro*. The specification does not provide guidance with respect to the capability, of the monoclonal

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antibodies with CCR2 specificity, to bind the CCR2 on the cell *in vitro* and/or *in vivo* and to block the HIV infection.

7) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to monoclonal antibodies with CCR2 specificity to have the capability to bind CCR2 and to block the HIV infection of the cell. There is lack of working examples regarding *in vivo* studies showing reduced viral loads or inhibition of HIV infection due to administration of monoclonal antibodies with specificity to CCR2.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

In conclusion, it is readily apparent from the aforementioned disclosure, in conjunction with a corresponding lack of scientific data and working embodiments regarding the method of treating HIV infection comprising administering monoclonal antibodies with specificity to CCR2, that one of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and accurately extrapolate whether monoclonal antibodies with specificity to CCR2 can be successfully used in the method of treating HIV infection.

Conclusion

Claim 55 is free of prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035.

The examiner can normally be reached on 9:00 AM to 5:30 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AB

Agnieszka Boesen, Ph.D.

9/28/06

A handwritten signature in black ink, appearing to read "Bruce Campell". The signature is fluid and cursive, with the first name "Bruce" and the last name "Campell" clearly distinguishable.

BRUCE R. CAMPPELL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600